EXHIBIT “G”

REVIEW

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Complications Associated with Sickle Cell Trait: A Brief Narrative Review

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ABSTRACT

Sickle cell trait occurs in approximately 300 million people worldwide, with the highest prevalence of approximately 30% to 40% in sub-Saharan Africa. Long considered a benign carrier state with relative protection against severe malaria, sickle cell trait occasionally can be associated with significant morbidity and mortality. Sickle cell trait is exclusively associated with rare but often fatal renal medullary cancer. Current cumulative evidence is convincing for associations with hematuria, renal papillary necrosis, hyposthenuria, splenic infarction, exertional rhabdomyolysis, and exercise-related sudden death. Sickle cell trait is probably associated with complicated hyphema, venous thromboembolic events, fetal loss, neonatal deaths, and preeclampsia, and possibly associated with acute chest syndrome, asymptomatic bacteriuria, and anemia in pregnancy. There is insufficient evidence to suggest an independent association with retinopathy, cholelithiasis, priapism, leg ulcers, liver necrosis, avascular necrosis of the femoral head, and stroke. Despite these associations, the average life span of individuals with sickle cell trait is similar to that of the general population. Nonetheless, given the large number of people with sickle cell trait, it is important that physicians be aware of these associations.

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Sickle cell trait is characterized by the inheritance of a normal hemoglobin gene (HbA) from 1 parent and an abnormal, mutated β_1-globin gene, the sickle hemoglobin gene (HbS), from the other parent.[1] In sickle cell disease, 2 abnormal allemorphic hemoglobin genes are inherited, of which at least 1 must be the sickle hemoglobin. In the homozygous sickle cell disease (HbSS), both abnormal hemoglobins are HbS. A normal adult hemoglobin is made from a combination of 2 β-globin protein chains with 2 α-globin chains and heme. The β_1-globin gene is located on the short arm of chromosome 11. Approximately 150 diseases have been linked to this same chromosome 11.

The sickle gene is multicentric in origin, and 4 main haplotypes, representing 4 different mutations, have been identified.[2] The Asian (Arabo-Indian) haplotype is thought to have originated in Central India or Saudi Arabia, the Benin haplotype originated in central West Africa, the Senegal haplotype originated in the West African region above the Niger river, and the Bantu (or CAR) haplotype originated in central and south central Africa. The haplotypes influence sickle cell disease severity. The Senegal haplotype, on average, is associated with the least severe disease, and the Bantu haplotype is associated with the most severe disease.[2] The influence of these haplotypes on complication rates in individuals with sickle cell trait is yet to be determined.

It is estimated that 300 million people worldwide carry the sickle cell trait, with the highest concentration in Africa and the Mediterranean region. Approximately 1 in 3 persons in West Africa and 1 in 5 persons (20%) in the eastern province of Saudi Arabia carry the sickle cell trait.[3,4] In the United States, the prevalence of sickle cell trait is estimated

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at approximately 8% in African-Americans and 0.05% in white Americans. Data from the newborn screening program in California suggest the incidence of sickle cell trait is approximately 7.9 per 100,000 newborns.[5]

Sickle cell trait can coexist with gene deletion α-thalassemia, particularly in blacks. There is a trimodal distribution of HbS levels in individuals with sickle cell trait, based on the number of α-globin genes. Individuals with sickle cell trait and normal α-globin genotype have approximately 40% HbS in their erythrocytes, whereas those with loss of 3 α-globin genes have 20% to 25% HbS. Those with loss of 1 α-globin gene (_α/αα genotype) have 35% HbS.[6]

Increased red blood cell sickling and polymerization can occur in sickle cell trait under conditions of severe tissue hypoxia, acidosis, increased viscosity, dehydration, and hypothermia. The severity of polymerization decreases in those with lower HbS concentration. In vitro studies have established that heterozygous sickle cell trait erythrocytes sickle when the oxygen level is decreased to 2% compared with 4% to 6% for homozygous erythrocytes.[7] The mean percentage of reversible sickling for sickle cell trait in military recruits who exercised to exhaustion in simulated elevations increased from 2% at elevations of 4050 ft to 8.5% at elevations of 13,123 ft.[8] At 0% oxygen saturation, approximately 35% of sickle cell trait cells sickle compared with 70% for HbSS.[9]

Traditionally, sickle cell trait has been viewed as a benign condition, a non-disease, partially protective against falciparum malaria and without any of the painful episodes characteristic of the homozygous sickle cell disease.[10,11] On a population basis, sickle cell trait has no discernible impact on life expectancy.[12] Hemoglobin and hematocrit values in individuals with sickle cell trait are similar to those of persons without hemoglobinopathy.[11,13] Individuals with sickle cell trait are eligible for blood donation in the United States and in many other countries.[14,15] The storage quality of sickle cell trait blood is good and comparable to that of HbAA blood.[16] However, current leukocyte-reduction filtration systems tend to be clogged by blood from sickle cell trait donors.[17]

Sickle cell trait is not completely benign. There is extensive literature describing the morbidity of sickle cell trait.[11] Much of the data were derived from case reports or uncontrolled observational studies. To attribute a specific complication to sickle cell trait, at a minimum, it must occur in greater frequency in individuals with sickle cell trait than in the general population. On the basis of the strength and specificity of observed associations with sickle cell trait, the complications can be grouped as definite, probable, or possible (Table 1). It is important that both physicians and persons with sickle cell trait become familiar with these potential complications so that prompt treatments can be offered when they occur, and preventive steps can be taken when and where appropriate.

CLINICAL SIGNIFICANCE

- Sickle cell trait is found in approximately 300 million people, with concentrations in Africa, the Arabian Peninsula, India, the Mediterranean, and the southern United States.
- Although largely a protective carrier state, sickle cell trait is associated with rare but fatal renal medullary cancer, exercise-related deaths, splenic infarction, hematuria, hyposthenuria, venous thromboembolism, complicated hyphema, and fetal loss.
- Knowledge of these associations is critical for appropriate management.

DEFINITE ASSOCIATIONS

Renal Medullary Carcinoma

Renal medullary carcinoma is a rare, aggressive tumor of the kidney that is seen almost exclusively in young individuals with sickle cell trait. It was first described in 1995 in a case series report of 34 patients, 33 of whom had sickle cell trait.[17] Approximately 120 cases have been reported to date.[18] Of these, only 1 patient is known not to have a positive sickling status. All patients except 1 were aged less than 40 years, with a median age of 22 years. There is a male preponderance (M: F of 3:1) before age 24 years and equal frequency by gender after age 24 years.

The tumor arises from the epithelium of distal collecting ducts and grows in an infiltrative pattern, invading the renal sinuses. Most of the tumors are found in the right kidney (3:1 comparing right with left kidneys). The tumor tends to be lobulated, firm, and poorly circumscribed. Cytology consists of a primary cohesive group of cells with vacuolated cytoplasm, displaced or indented nuclei, and prominent nucleoli. The tumor demonstrates lack of chromosomal imbalance and has distinct molecular signature compared with renal cell cancer. In 1 case, chromosome 11, the same chromosome that carries the β-globin gene, was monosomic in all cells analyzed. Beckwith-Wiedeman syndrome and multiple tumor-associated chromosome region 1, similarly localized to chromosome 11p15.5, are associated with renal cancer.

Hematuria and flank pain are the most common initial symptoms. Most tumors can be detected with computed tomography or magnetic resonance imaging. In almost all patients, the disease is disseminated at the time of diagnosis. The median survival is approximately 15 weeks. Only 3 patients appear to have survived the disease, with the longest reported survival of 8 years. Management options include radical nephrectomy, chemotherapy using regimens for transitional and renal cell carcinomas, and palliative radiation therapy.[19]

Hematuria and Renal Papillary Necrosis

Hematuria, both microscopic and macroscopic, is the most frequent complication of sickle cell trait.[11,20,21] Hematuria accounted for 4% of hospitalizations for sickle cell trait in male

Table 1 Complications Associated with Sickle Cell Trait

Definite Associations
Renal medullary cancer
Hematuria
Renal papillary necrosis
Hyposthenuria
Splenic infarction
Exertional rhabdomyolysis
Exercise-related sudden death
Protection against severe falciparum malaria
Probable Associations
Complicated hyphema
Venous thromboembolic events
Fetal loss/demise
Low birthweight
Possible Associations
Acute chest syndrome
Asymptomatic bacteriuria in pregnancy
Proliferative retinopathy
Unlikely or Unproven Associations
Stroke
Cholelithiasis
Priapism
Leg ulcers
Avascular necrosis of the femoral head

African-Americans admitted to Veterans Administration hospitals compared with a hematuria admission rate of 2% among male African-Americans with normal hemoglobin.[20] Many cases (~50%) are due to renal papillary necrosis.[22] Other causes, such as infection, stones, von Willebrand's disease, or malignancy, account for the remaining cases. Renal papillary necrosis results from local microinfarctions in the renal medulla.[22] The hypoxemia, hypertonicity, acidosis, and hyperthermia of arterial blood passing through the long vasa recta of the renal medulla, a consequence of the countercurrent exchange in the renal medulla,[23] promote polymerization of deoxyhemoglobin S.

Renal papillary necrosis presents with painless gross hematuria. The left kidney is more frequently involved primarily because of its larger size and the higher venous pressure from the compression of the left renal vein on the iliac crest between the aorta and the superior mesenteric artery. The bleeding is most often mild, but it can be severe. Bleeding recurrence is common. Diagnosis is difficult to establish. Although the presence of sloughed papillae in the urine is pathognomic, it is less frequently seen. Diagnostic yield is increased by the use of cystourethroscopy, computed tomography, ultrasound, or intravenous pyelogram. The hematuria associated with renal papillary necrosis is commonly managed conservatively with bed rest, intravenous hydration, and alkalinization of the urine.[24] For severe bleeding, direct urethroscopic tamponade or fulguration, epsilon aminocaproic acid, or desmopressin acetate infusion may be required. Renal papillary necrosis is often complicated by urinary tract infection and obstruction.

Hyposthenuria

Hyposthenuria, the relative loss of the concentrating ability of the kidney, occurs as a result of repetitive microinfarctions in the renal medulla and changes in the renal blood flow. Hyposthenuria is progressive with age and is less severe in those with coexisting α-thalassemia.[25] Hyposthenuria is least severe in those with loss of 3 α-globin genes ($-/-\alpha$), followed in order by the ($-\alpha/-\alpha$), ($-\alpha/\alpha\alpha$) genotypes and most severe in those individuals with sickle cell trait with normal α-globin genotype.[25] Hyposthenuria results in obligatory loss of free water. When not compensated for with adequate fluid intake, hyposthenuria would increase the osmolality of the blood. Hyposthenuria contributes to the exertional heat illness and exercise-related death of young persons with sickle cell trait.[26]

Splenic Infarcts

Splenic infarcts in sickle cell trait are more common in the setting of exposure to low oxygen tension at high altitudes, including flight in unpressurized aircraft cabins or exercise in mountainous areas in those not acclimatized to such areas.[27-29] A majority of the cases have been in men, nonblacks, and patients with greater than 40% HbS at the time of incidence.[29] In most cases, splenic infarcts are mild and self-limited; however, in its most dramatic form, patients present with acute splenic syndrome, characterized by a triad of severe abdominal pain, splenomegaly, and left upper quadrant tenderness. Signs of peritoneal irritation, rebound tenderness, guarding, and rigidity may occur. Left pleural effusion and atelectasis develop in many of these patients. Increased levels of bilirubin, serum lactate dehydrogenase, reticulocytosis, and anemia may be seen. Splenic rupture may occur, necessitating emergency splenectomy. A few patients with acute splenic syndrome, whose sickling status was unknown at the time of presentation, underwent splenectomy.[29] In all of these cases, the spleens were enlarged from vascular congestion and hemorrhagic infarcts. Sickled cells were abundant in the congested vasculature of the splenic red pulp. Most cases of splenic infarction, including acute splenic syndrome, can be successfully managed with hydration, analgesia, rest, oxygen, and other supportive measures. Splenectomy is indicated mainly in cases of splenic rupture with significant intraperitoneal bleed, splenic abscess, and symptomatic massive splenomegaly, and for refractory sequestration crisis in patients with coexisting spherocytosis.

Exercise-related Deaths

Exercise-related deaths, although rare, occur at higher rates in individuals with sickle cell trait.[30-32] These deaths result from exercise-related rhabdomyolysis, heat stroke, acute renal failure, disseminated intravascular coagulation, and cardiac arrhythmia. The most convincing data have come

from studies of the US military. In 1987, Kark et al[31] found approximately a 28-fold increased risk of exercise-related deaths (relative risk = 27.6; 95% confidence interval [CI], 9-100; $P < .001$), unexplained by preexisting illness, among US Army recruits with sickle cell trait compared with those without sickle cell trait in their cohort study of 2 million enlisted recruits.[31] The rate of sudden unexplained deaths was 32.2 per 100,000 among the black recruits with sickle cell trait compared with 1.2 per 100,000 among black recruits without sickle cell trait. These findings have been corroborated by a similar study by Drehner et al[32] of nontraumatic deaths in the US Air Force between 1956 and 1996. They reported a relative risk for death of 23.5 (95% CI, 19.5-30.0) among personnel with sickle cell trait compared with those without sickle cell trait. There have been numerous (>30) case reports describing fatal or serious complications of exercise in young black men with sickle cell trait. It has been suggested that dehydration, hyperthermia, and acidosis resulting from the vigorous physical activity induce polymerization of the HbS, leading to vascular occlusion and endothelial damage. These in turn lead to a cascade of events, including rhabdomyolysis, myoglobinuria, acute renal failure, release of vasoactive substances, disseminated intravascular coagulation, and coronary vasoconstriction. Effective prevention includes gradual buildup of performance levels, adequate hydration, including ingestion of salt and potassium in exercise situations with excessive sweating, and cessation of activity with onset of muscle cramping, fatigue, and shortness of breath. Sickling collapse is managed as a medical emergency with high-flow oxygen administration, saline infusion for presumed rhabdomyolysis, and appropriate use of external defibrillation.[33]

Decreased Malaria Deaths

Allison[34] first suggested the relative protection of sickle cell trait against falciparum malaria in 1954. He noted that whereas 14 of 15 individuals without sickle cell trait developed malaria when inoculated with *Plasmodium falciparum*, only 2 of 15 individuals with sickle cell trait developed malaria when similarly inoculated. Subsequently, numerous studies have confirmed this high degree of resistance to severe *falciparum* malaria.[35] Also, whereas the rate of severe or complicated *falciparum* malaria requiring acute hospitalization decreased by approximately 90% in individuals with sickle cell trait, there was no significant reduction in the prevalence of symptomless parasitemia.[35] The protection appears to increase with age from only 20% in the first 2 years of life to a maximum of 56% by the age of 10 years and decreasing to 30% in those aged more than 10 years.[35] Proposed protective mechanisms include reduced parasite growth and enhanced removal of parasitized cells through innate and acquired immune processes.[36] The protection is specific for *falciparum* malaria and not any of the other 3 types of malaria (*Plasmodium vivax, Plasmodium ovale, and Plasmodium malariae*).[35]

PROBABLE ASSOCIATIONS

Venous Thromboembolic Events

Data from a case-control study of 1070 black patients and a retrospective cohort study of 65,000 consecutive hospitalizations of black men suggest that individuals with sickle cell trait have higher rates of venous thromboembolic events (deep vein thrombosis or pulmonary embolism) compared with similar blacks with normal hemoglobin.[37,38] In the case-control study, persons with sickle cell trait had approximately a 4-fold increased risk for pulmonary embolism (odds ratio = 3.9; 95% CI, 2.2-6.9) and approximately a 2-fold (odds ratio 1.8; 95% CI, 1.2-2.9) risk of combined deep vein thrombosis or pulmonary embolism.[37] The increases were observed for idiopathic and provoked venous thromboembolism, as well as for first and recurrent venous thromboembolism. In the retrospective study, pulmonary embolism occurred in 2.2% of patients with sickle cell trait compared with 1.5% of patients with normal hemoglobin.[38] Compared with matched controls with normal hemoglobin, individuals with sickle cell trait have increases in the measures of coagulation activity.[39] Individuals with sickle cell trait had significantly higher levels of d-dimers, thrombin-antithrombin complexes, and prothrombin fragment 1.2, and their absolute blood monocyte levels were increased. Monocytes play an active role in endothelial damage, atherogenesis, and plaque rupture, thereby promoting the thrombotic diathesis. The heightened hypercoagulable state might explain some of the thromboembolic phenomena described with sickle cell trait. We recommend effective thromboprophylaxis (with low-molecular-weight heparin, low-dose unfractionated heparin, fondaparinux, or intermittent pneumatic compression) in all hospitalized patients with sickle cell trait and particularly after gynecologic, urologic, or orthopedic surgical procedures.

Pregnancy-related Complications

Pregnant patients with sickle cell trait appear to be at increased risk for fetal loss, low birth weight, and pre-eclampsia compared with women with normal hemoglobin.[40,41] In a retrospective case-control study of pregnancies exceeding 16 weeks' gestation, the average duration of pregnancy and birth weight were significantly lower for patients with sickle cell trait in comparison with a cohort of women with normal hemoglobin. The rate of fetal death also was significantly higher (9.7% vs 3.5%; $P = .015$). Placental abnormalities might play a causal role, because the study women had more frequent acute ascending amniotic infection and meconium histiocytosis. Also, sickling in the intervillous space and decidual vessels was found in the patients with sickle cell trait.[40] A prospective study by Larabee and Monga[41] demonstrated that the rate of preeclampsia was significantly increased in patients with sickle cell trait (24.7% vs 10.3%, $P < .0001$).[41] There also was a statistically significant decrease in gestational age at delivery, lower birth weight, and an increase in the rate of postpartum endometritis.

Complicated Hyphema

Secondary hemorrhage, increased intraocular pressure, central retinal artery occlusion, and optic nerve atrophy tend to complicate traumatic hyphema in patients with sickle cell trait.[42] The complications are often out of proportion to the size of the hyphema. Conditions in the aqueous humor are conducive to erythrocyte sickling. The sickled red blood cells block the trabecular meshwork, leading to increased intraocular pressure. This leads to further stagnation of blood in the microvasculature, excessive deoxygenation, and more sickling. Management includes aggressive intraocular pressure reduction with beta-adrenergic agents, application of topical steroids, and early anterior chamber washout. Transcorneal oxygen therapy (using humidified oxygen at a flow rate of 1-3 L/min) and hyperbaric oxygen have been used in some centers. Acetazolamide and hyperosmotic/diuretic agents can worsen the sickling process and should be avoided.

POSSIBLE ASSOCIATIONS

Retinopathy

There have been isolated reports of proliferative retinopathy in individuals with sickle cell trait, the majority of whom had coexisting diabetes mellitus or other systemic disease capable of explaining the retinopathy. Complete ophthalmologic examination, including fluorescein angiography, of individuals with sickle cell trait in Ivory Coast found retinal lesions in 70% of the patients. Approximately 49% had nonvasoproliferative lesions, 22.7% had proliferative lesions, and 2.7% had neovascular lesions.[43] However, there was no comparison group and no data were provided on the co-occurrence of diabetes mellitus or other systemic diseases in the study population. A similar complete ophthalmologic examination of 32 healthy individuals with sickle cell trait in Canada found no case of retinopathy.[44]

Acute Chest Syndrome

On exclusion of cases of pneumonia as a cause of new pulmonary infiltrates, there have been 7 case reports of acute chest syndrome in patients with sickle cell trait.[45] Three of these were perioperative complications. One occurred after a bicycle accident, and one occurred in the setting of a hyperosmolar state induced by diabetes. The settings of the remaining 2 cases were not mentioned.

Asymptomatic Bacteriuria

Earlier studies reported a significantly higher incidence of asymptomatic bacteriuria in pregnant patients with sickle cell trait compared with pregnant patients with normal hemoglobin;[46] however, a recent retrospective cohort study by Thurman et al[47] disputes this. Whereas pregnant women with sickle cell trait were no more susceptible to asymptomatic bacteriuria or acute cystitis, they did have higher rates of pyelonephritis, but this was confounded by the fact that many of these patients had secondary risk factors, such as previous pyelonephritis or noncompliance with therapy.

INSUFFICIENT EVIDENCE

There are several reports of other abnormalities with implied association with sickle cell trait. These include anemia, cholelithiasis, stroke, higher prevalence of diabetic retinopathy and albuminuria, priapism, leg ulcers, avascular necrosis of the femoral head, and liver necrosis. The data remain unconvincing or insufficient to draw a meaningful association at this time.

CONCLUSIONS

Although sickle cell trait is a benign condition in a majority of affected individuals, current evidence suggests convincing associations with renal medullary carcinoma, hematuria, renal papillary necrosis, hyposthenuria, splenic infarction, and exercise-related deaths, and probable or possible associations with thromboembolic disease, pregnancy-related complications, complicated hyphema, and acute chest syndrome. Many of these associations are relatively uncommon or occur under conditions of severe tissue hypoxia, acidosis, increased viscosity, dehydration, or hypothermia. It is possible that some of these disorders are related to the linkage of the β-globin gene to other disease loci on chromosome 11. Physicians and patients should be well educated on these possibilities.

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